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EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
05/06/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/521,410	ULLRICH ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 17-39* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 22-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-14,17-21 and 35-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/03/2010 has been entered.

2. Claims 1-14 and 17-39 are pending.

3. Claims 1-9 and 22-34 have been previously withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions protein as previously set forth in the Office Action of October 19, 2007.

4. The species restriction for Group 2 set forth in the Requirement for Restriction of 06/01/2007 is withdrawn and claims 11, 13, 20, and 21 are rejoined for examination.

5. Claims 10-14, 17-21, and 35-39 are currently under consideration.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 10-14, 17-21, and 35-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing the invasivity of cancer cells in a subject in need thereof comprising administering to the subject an inhibitor of the

AXL protein selected from the group consisting of anti-AXL antibodies or Fab, Fab', Fab2 or scFV antigen binding fragments thereof or an inhibitor of GAS6 selected from the group consisting of anti-GAS6 antibodies or Fab, Fab', Fab2 or scFV antigen binding fragments thereof, and wherein said cancer cells are selected from the group consisting of breast cancer cells, prostate cancer cells, kidney cancer cells, glioblastoma cells or cancer cells of epithelial origin, *does not* reasonably provide enablement for a method of reducing the invasivity of cancer cells in a subject in need thereof comprising administering to the subject an inhibitor of the AXL gene, AXL ligand gene, AXL protein or AXL protein ligand, or any combination thereof, in an amount which is effective for reducing the invasivity of cancer cells, and wherein said inhibitor of the AXL protein is selected from the group consisting of anti-AXL antibodies or Fab, Fab', Fab2 or scFV antigen binding fragments thereof, and wherein said cancer cells are selected from the group consisting of breast cancer cells, prostate cancer cells, kidney cancer cells, glioblastoma cells or cancer cells of epithelial origin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4)

the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are broadly drawn to a method of reducing the invasivity of cancer cells in a subject in need thereof comprising administering to the subject an inhibitor of the AXL gene, AXL ligand gene, AXL protein or AXL protein ligand, or any combination thereof, in an amount which is effective for reducing the invasivity of cancer cells, and wherein said inhibitor of the AXL protein is selected from the group consisting of anti-AXL antibodies or Fab, Fab', Fab2 or scFV antigen binding fragments thereof, and wherein said cancer cells are selected from the group consisting of breast cancer cells, prostate cancer cells, kidney cancer cells, glioblastoma cells or cancer cells of epithelial origin.

The specification teaches that the inhibitor of the AXL gene, AXL ligand gene, AXL protein or ligand thereof, e.g. GAS6, may be an antibody, a biologically active nucleic acid or a low molecular weight compound, e.g. a peptide or a non-peptidic organic compound. See p. 6.

The specification teaches that in a preferred embodiment the inhibitor is an antibody directed against the AXL protein or a ligand thereof, e.g. GAS6. The term "antibody" relates to polyclonal antibodies and monoclonal antibodies, particularly to chimeric or humanized monoclonal antibodies or to human antibodies. Further, the term comprises antibody fragments, e.g. proteolytic fragments such as Fab, Fab' or F(ab)2 fragments or recombinant fragments such as single chain antibody fragments, e.g. scFv fragments. Methods of manufacturing antibodies or antibody fragments as described above are known in the art. See p. 6-7

The specification teaches that in a further preferred embodiment the inhibitor is a biologically active nucleic acid, e.g. a DNA, an RNA or a synthetic nucleic acid analog.

Preferred examples of biologically active nucleic acids are antisense nucleic acids, ribozymes or RNA interference molecules directed against the AXL gene or an AXL ligand gene or a transcript thereof. A further preferred example of a biologically active nucleic acid is a dominant-negative mutant of the AXL gene. Biologically active nucleic acids may be delivered by known procedures, e.g. by using viral or non-viral gene transfer vectors. See p. 7.

The specification teaches that in a further preferred embodiment the inhibitor is a peptidic compound, e.g. a peptide having a length of from 4 to 25 amino acids, a cyclic peptide, a peptide, derivative or a peptide mimetic derived from such a peptide. Alternatively the low-molecular weight inhibitor may be a non-peptidic, organic compound, e.g. an inhibitor of AXL kinase activity. Low-molecular weight inhibitors may be obtained by screening suitable compound libraries in a method as described, in more detail below. See p. 7.

The specification places no limitation on the AXL protein ligands or the genes that encode them. Thus, given the above, the claims encompass using a large genus of inhibitors of the AXL gene, AXL ligand gene, and AXL protein ligand to reduce invasivity of cancer cells in a subject

The specification teaches that overexpression of the receptor tyrosine kinase AXL/UFO (Genbank accession No. M 76125) has been implicated in the development of human hematological malignancies. Further, very recent data indicate that signaling of AXL and its ligand GAS6 is involved in angiogenesis, adhesion and survival of cancer cells, see p.1, lines 15-19.

The specification teaches that the present invention relates to the diagnosis or the prevention and/or treatment of malignant disorders, particularly the tumor invasivity and/or

metastasis formation in malignant disorders. Preferred examples of malignant disorders are cancers of the breast, prostate, kidney, colon, lung and glioblastomas. More preferably, the malignant disorder-is breast cancer or glioblastomas, see p. 5, lines 14-19.

The specification teaches that Axl mRNA was expressed in primary breast cancer tumors, and other tumors and cancer cell lines (kidney, prostate and glioblastomas) as well, see p. 25, line 22 to p. 26, line 10 and Fig. 2-4.

The specification teaches that an antibody to the extracellular domain of Axl or dominant negative mutant of AXL (dnAXL) transduced by retrovirus can inhibit the migration and invasion of breast cancer cell lines and a prostate cancer cell line into Matrigel in a Boyden chamber *in vitro* assay, see p. 21-26, and figures 5-7.

The specification teaches that dnAXL transfected glioblastoma cells exhibited inhibited growth and invasion *in vivo* and *in vitro*. See p. 32-36 and Fig. 8-11.

One cannot extrapolate the teachings of the specification to the enablement of the claims because a nexus has not been established between inhibiting Axl gene, Axl ligand gene, and Axl protein ligand with the broadly contemplated and claimed inhibitors thereof because the development of therapeutics for cancer and the design and delivery of inhibitors is well known in the art to be unpredictable and without further guidance one of skill in the art would not be able to make and use the broadly claimed method without undue experimentation..

As drawn to the unpredictability of drug development for cancer, Gura (Science, 1997, 278:1041-1042, previously cited) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have

shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Furthermore, Kaiser (Science, 2006, 313: 1370, previously cited) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para. Thus, given the above, in absence of further guidance on making and using the broadly claimed inhibitors , one of skill in the art could not make and use the method used for the reducing the invasivity of cancer cells without undue experimentation.

Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65, previously cited) teaches that tumors resist penetration by drugs (p.58, col. 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col. 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39, previously cited) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col. 2). In addition the inhibitors must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the cancer and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of inducing invasion despite action at

the proper site for the inhibitors. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The inhibitors may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half-life of the antibody. In addition, the inhibitors may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where it has no effect, circulation into the target area may be insufficient to carry the antibody and a large enough local concentration may not be established. Thus, given the breadth of the claimed inhibitors, in the absence of sufficient guidance for make and using these inhibitors for reducing the invasivity of cancer cells, and given the unpredictability in the art, one of skill in the art would not be able to make and use the method as broadly claimed without undue experimentation.

Additionally, as drawn to nucleic acid inhibitors of the Axl gene or Axl ligand gene the art teaches that are problems with these technologies making their use unpredictable without sufficient guidance and direction. For example, Gura (Science, 1995, 270:575-577) teaches that researchers have many concerns with the antisense therapy. Gura discloses that "the biggest concern is that antisense compounds simply don't work the way researchers once thought they did." Other drawbacks in animal studies include difficulty getting antisense oligonucleotides to target tissues and the existence of potentially toxic side effects such as increased blood clotting and cardiovascular problems (page 575, col. 1, para 2). Another problem stems from the fact that oligonucleotides used as controls produced the same biological effects in cell culture as did the antisense compounds (page 576, col. 1, para. 2 and 3). In addition, Gura reports problems

with synthetic antisense oligonucleotides in that unwanted and sometimes lethal side effects occurred in animal experiments, and that they block cell migration and adhesion to underlying tissue in vitro (page 576, col.3, para.1 and 3). Thus a high degree of unpredictability is associated with the use of antisense constructs employed in methods of inhibiting expression of a particular gene *in vivo*. Additionally, Scherer and Rossi (Nature Biotechnology 2003, 21: 1457-1465) teach that the challenges that need to be meet for therapeutic use of anti-sense technologies like antisense oligonucleotides, RNA interference, and ribozymes include obtaining efficient delivery, enhancing stability, minimizing off target effects and identification of sensitive sites in the RNA target. See Abstract. Scherer and Rossi teach that finding an effective target site in mRNA for these anti-sense technologies can be problematic, with the major limitation being identification of sequence/antisense combination that provides potent knockdown of the target RNA at a low concentration of antisense agent. See ¶ bridging p. 1461-1462. Scherer and Rossi teach that off target effects of these anti-sense technologies is another problem, which could lead to unwanted side effects when using anti-sense technologies. See 1462-1463. Additionally, Scherer and Rossi teach that efficient delivery is the limiting factor for use of the antisense compounds and, as of publication of the article; there was no single reagent or modification that can be effectively used for all the different antisense agents. See p. 1463-1st col. Thus, in absence of sufficient guidance and/or exemplification for targeting the Axl gene or Axl ligand gene with the broadly completed inhibitors, including nucleic based inhibitors, undue experimentation would be required to make and use the method as broadly claimed.

Furthermore, the use of the antisense technologies and the dominant negative mutant of the Axl gene encompass using vectors and delivery methods that fall under gene therapy

technologies. Gene therapy using administration of recombinant nucleic acids involving *in vivo* or *ex vivo* methods had seen little success at the time the invention was made despite a great deal of work and resources. Several reviews in the art show that difficulties with vector selection, mode of delivery and persistence of predictable and effective levels of expression of the protein, created technical barriers to the practice of gene therapy methods. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" Verma et al. ((1997) Nature Volume 389, page 239, column 3, and paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed-remain a nagging problem for the entire field", and that "many problems must be solved before gene therapy will be useful for more than the rare application" Marshall ((1995) Science, Volume 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al. (Goodman & Gilman's The Pharmacological Basis of Therapeutics (1996), 9th Edition, Chapter 5, McGraw-W, NY) explains, "the delivery of exogenous DNA and its processing by target cells requites the introduction of new pharmakinetic paradigms beyond those that describe the conventional medicines in use today". Eck et al. teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the in *vivo* consequences of altered gene expression and protein function, the fraction taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and

stability of the protein produced, and the protein's compartmentalization within the cell or its secretory fat, once produced. These factors differ dramatically based on the vector used, the protein being produced and the disease being treated (see Eck et al. bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al. teaches, in reference to *ex vivo* methods, that weak promoters produce only low levels of therapeutically effective protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, ". . . the search for such combinations is a case of trial error for a given cell type" (Verma et al., *supra,* page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al. Human Gene Therapy, l996, Volume 7, pages 1781-1790, see page1789, column 1, first paragraph). Thus, the art at the at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect in vivo by expressing a therapeutic gene using any of the expression constructs known in the art was extremely low.

More recently, Rubanyi (Mol. Aspects Med. (2001) 22:113-142) teaches that the problems described above remain unresolved. Rubanyi states, "[although theoretical advantages of human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." See page 113, paragraph 1. Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in

gene expression control systems (see section 3. "Technical hurdles to be overcome in the future", beginning on page 116 and continued through page 125). Furthermore, Juengst (British Medical Journal (2003) Volume 326, pages 1410-1411) teaches the unpredictable nature of gene therapy and that a few of the apparent successes actually developed T cell-acute lymphoblastic leukemia due to insertional mutagenesis at or near the LMO-2 gene causing altered gene expression. The art has demonstrated that a large amount of experimentation has already been performed without demonstrating successful gene therapy methods for treatment of disease.

Thus, in order to practice the claimed invention, the skilled artisan would not have found sufficient guidance in the specification to achieve effective levels of the expressed nucleic acid, to select a proper dose or administration route or to determine other factors for a successful treatment. The prior art did not compensate for the lack of guidance in the specification since the teachings do not recognize any clearly successful gene therapy methods. The skilled artisan would have had to engage in a large amount of experimentation to practice the claimed invention. In view of the lack of guidance and the large amount of experimentation in an unpredictable art, it would require undue experimentation to practice the claimed invention.

Given the above, in the absence sufficient guidance and direction demonstrating reduction of invasivity of cancers with the broadly claimed inhibitors to the Axl gene, Axl ligand gene and Axl ligand protein, one of skill in the art could not predictably practice the claimed invention without undue experimentation.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the stare of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA

1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides insufficient working examples which would provide guidance to one skilled in the art and insufficient evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, undue experimentation would be required to practice the claimed invention.

8. Claims 10-14, 17-20, and 35-38 are rejected as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a method of reducing the invasivity of cancer cells in a subject in need thereof comprising administering to the subject an inhibitor of the AXL gene,

AXL ligand gene, AXL protein or AXL protein ligand, or any combination thereof, in an amount which is effective for reducing the invasivity of cancer cells, and wherein said inhibitor of the AXL protein is selected from the group consisting of anti-AXL antibodies or Fab, Fab', Fab2 or scFV antigen binding fragments thereof, and wherein said cancer cells are selected from the group consisting of breast cancer cells, prostate cancer cells, kidney cancer cells, glioblastoma cells or cancer cells of epithelial origin.

The specification teaches that the inhibitor of the AXL gene, AXL ligand gene, AXL protein or ligand thereof, e.g. GAS6, may be an antibody, a biologically active nucleic acid or a low molecular weight compound, e.g. a peptide or a non-peptidic organic compound. See p. 6.

The specification teaches that in a preferred embodiment the inhibitor is an antibody directed against the AXL protein or a ligand thereof, e.g. GAS6. The term "antibody" relates to polyclonal antibodies and monoclonal antibodies, particularly to chimeric or humanized monoclonal antibodies or to human antibodies. Further, the term comprises antibody fragments, e.g. proteolytic fragments such as Fab, Fab' or F(ab)2 fragments or recombinant fragments such as single chain antibody fragments, e.g. scFv fragments. Methods of manufacturing antibodies or antibody fragments as described above are known in the art. See p. 6-7

The specification teaches that in a further preferred embodiment the inhibitor is a biologically active nucleic acid, e.g. a DNA, an RNA or a synthetic nucleic acid analog. Preferred examples of biologically active nucleic acids are antisense nucleic acids, ribozymes or RNA interference molecules directed against the AXL gene or an AXL ligand gene or a transcript thereof. A further preferred example of a biologically active nucleic acid is a dominant-negative mutant of the AXL gene. Biologically active nucleic acids may be delivered

by known procedures, e.g. by using viral or non-viral gene transfer vectors. See p. 7.

The specification teaches that in a further preferred embodiment the inhibitor is a peptidic compound, e.g. a peptide having a length of from 4 to 25 amino acids, a cyclic peptide, a peptide, derivative or a peptide mimetic derived from such a peptide. Alternatively the low-molecular weight inhibitor may be a non-peptidic, organic compound, e.g. an inhibitor of AXL kinase activity. Low-molecular weight inhibitors may be obtained by screening suitable compound libraries in a method as described, in more detail below. See p. 7.

The specification places no limitation on the AXL protein ligands or the genes that encode them. Thus, given the above, the claims encompass using a large genus of inhibitors of the AXL gene, AXL ligand gene, and AXL protein ligand to reduce invasivity of cancer cells in a subject and a large genus of AXL ligands and AXL ligand genes. The genus of inhibitors and genus of AXL ligands and AXL ligand genes are highly diverse, with the members varying significantly both in structure and function. The description of a polyclonal antibody directed to the extracellular portion of AXL that inhibits the migration of cell lines *in vitro* (see p. 26-lines 24-28 and Fig. 6) and the dominant negative mutant of Axl (See p. 32-36 and Fig. 8-11) fails to adequately describe the genus of inhibitors because said genus tolerates members which differ significantly in both structure and function from said antibody to AXL protein or the dnAXL. Additionally, the description of GAS6 does not provide adequate support for the genus of AXL protein ligands and AXL ligand genes. One of skill in the art can reasonably conclude that applicant was not in possession of the genus inhibitors of the AXL gene, AXL ligand gene, and AXL protein ligand and the genus of AXL protein ligands or AXL ligand genes at the time the invention was filed. Because the genus of inhibitors of the AXL gene, AXL ligand gene, and

AXL protein ligand and the genus of AXL protein ligand and AXL ligand gene are not adequately described, the method claims relaying on said genera are also not adequately described.

As it is drawn to the DNA arts, the findings in *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

It is noted that as of the filing date antibodies that inhibit AXL protein activity and GAS6 were known in the art (see U.S. Pat. No. 5,468,634 col. 7, line 60 to col. 8 line 30, previously cited, and USPN 5,538,861), however, this fail to adequately describe an entire genus because the genus is highly variant encompassing members which differ significantly in structure from the few art known inhibitors or GAS6.

In the instant case the genus is only described as a definition by function (i.e. inhibition of AXL gene, AXL ligand protein or gene or binding of AXL), and beyond the example of antibodies and dnAxl or GAS6, one of skill in the art cannot readily visualize or recognize the identity of members of the genus or know what that material consists of.

Additionally, the following teaching of the Federal Circuit as set out in *Noelle v. Lederman*, 69 USPQ2d 1508 (Fed. Cir. 2004) 355 F3d 1343 clearly applies to the instant claimed invention as drawn to antibodies or fragments to the broadly the broadly claimed Axl protein ligand. The court teaches as follows: "Noelle did not provide sufficient support for the claims to the human CD40CR antibody in his '480 application because Noelle failed to disclose the structural elements of human CD40CR antibody or antigen in his earlier '799 application. Noelle argues that because antibodies are defined by their binding affinity to antigens, not their physical structure, he sufficiently described human CD40CR antibody by stating that it binds to human CD40CR antigen. Noelle cites Enzo Biochem II for this proposition. This argument fails, however, because Noelle did not sufficiently describe the human CD40CR antigen at the time of the filing of the '799 patent application. In fact, Noelle only described the mouse antigen when he claimed the mouse, human, and genus forms of CD40CR antibodies by citing to the ATCC number of the hybridoma secreting the mouse CD40CR antibody. If Noelle had sufficiently

described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. Noelle did not describe human CD40CR antigen. Therefore, Noelle attempted to define an unknown by its binding affinity to another unknown. As a result, Noelle's claims to human forms of CD40CR antibody found in his '480 application cannot gain the benefit of the earlier filing date of his '799 patent application. Moreover, Noelle cannot claim the genus form of CD40CR antibody by simply describing mouse CD40CR antigen". *Noelle v. Lederman*, 69 USPQ2d 1508 (Fed. Cir. 2004) 355 F3d 1343 at 1514.

Thus to satisfy the written description requirement for the broadly claimed genus of the Axl ligand proteins bound by the antibodies must be adequately described. The Federal Circuit further addresses this issue in *In re Alonso*, 88 USPQ2d 1849 (Fed. Cir. 2008) 545 F3d 1015, "The specification of the '749 Application does not characterize the antigens to which the monoclonal antibodies must bind; it discloses only the molecular weight of the one antigen identified in Example 2. This is clearly insufficient. The specification teaches nothing about the structure, epitope characterization, binding affinity, specificity, or pharmacological properties common to the large family of antibodies implicated by the method. While Alonso's claim is written as a method, the antibodies themselves are described in purely structural language — "a monoclonal antibody idiotypic to the neurofibrosarcoma of said human." This sparse description of antibody structure in the claim stands in stark contrast to the detailed method of *making* the antibodies found in the specification" *In re Alonso*, 88 USPQ2d 1849 (Fed. Cir. 2008) at 1853.

The instant specification has only described GAS6, thus it fails to describe the genus of antibodies to the AXL protein ligand. Therefore, since the claims encompass a genus based on

unknown AXL protein ligands, it is unclear what structures would identify members of the genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genera, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolation. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Thus, given the above, the specification does not provide an adequate written description of the genus of inhibitors of the AXL gene, AXL ligand gene, and AXL protein ligand and the genus of AXL protein ligand and AXL ligand gene

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claim 10, 11, 18, 20, 35, and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/48190 A2 (Orum et al. 5 July 2001).

WO 01/48190 teaches using LNA modified anti-sense oligonucleotides to the AXL gene to treat cancer of the prostate, brain, intestine, lung, liver, ovaries, and testes in humans and mammals. See Table 1, claims 1-12, p. 4-lines 19-33, p. 7-lines 1-25. WO 01/48190 teaches targeting genes involved in invasion and metastasis. See p. 14. It is noted that claim 11 does not limit the inhibitor used, but simply states what the protein ligand for AXL is.

Although the reference does not specifically state that the method is a method of reducing the invasivity of cancer cells, given that prostate cancer patients are a subject in need of reduced invasivity of cancer cells and an inhibitor of the AXL gene is being administered to that population, the claimed method appears to be the same as the prior art method, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977).

10. Claim 10-14, 18-20, and 35-39 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/30964 A2 (Burmer et al. 3 May 2001).

WO 01/30964 teaches using anti-sense and ribozyme oligonucleotides to the AXL gene and antibodies to the AXL protein (including $F(ab)_2$, Fab', Fab, and sc FV fragments) to treat cancer and reduce metastasis of the liver, kidney, breast, colon or prostate in humans and reduce

the expression of Axl. See Claims 10-12, Table 1-p.66, p. 4-lines 4-25, p. 5-8, p. 12-lines 13-15, p. 30-lines 1-5 and p. 35-39.

Although the reference does not specifically state that the method is a method of reducing the invasivity of cancer cells or inhibiting AXL protein activity or interaction with its ligand, given that prostate and kidney cancer patients are a subject in need of reduced invasivity of cancer cells and an inhibitor of the AXL gene/protein is being administered to that population, the claimed method appears to be the same as the prior art method, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 10-12, 14, 18, 19, 35, 36, 38 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over USPN 5,468,634 (Liu E. T. 1995, previously cited) in view of WO 89/06692 (Hudziak et al. 1989), in further view of USPN 5,538,861 (Schneider et al. 1996) and in further view of Jacob et al. (Cancer Detection and Prevention 1999, 23:325-332).

USPN 5,468,634 teaches using an antibody that inhibits Axl receptor function for therapeutic purposes in methods described by WO 89/06692. USPN 5,468,634 teaches that inhibition can be achieved with an antibody blocks receptor function or stimulates receptor function through down regulation. USPN 5,468,634 teaches using antibodies to the extracellular domain conjugated to ricin A chain for therapeutic purposes. See ¶ bridging col. 7 and 8. USPN 5,468,634 teaches that $F(ab)_2$, Fab', and Fab fragments of the anti-Axl antibody. Sec. col. 7-lines 30-60. USPN 5,468,634 teaches that Axl was seen in most human cell lines tested, including breast cancer cell lines. Sec Col. 16 and Table 1.

USPN 5,468,634 does not specifically teach reducing the invasivity of cancers in subject with cancers cells of the breast, prostate, kidney, glioblastoma, or cancer cells of epithelial origin.

WO 89/06692 teaches treating inhibiting the growth and metastasis of tumor cells, including breast cancer, with antibodies that inhibit growth factor receptor function, antibodies that inhibit the function of the receptor ligand, and antibodies to the receptor conjugated to cytotoxic moieties. See abstract, p. 8-line 20 to p. 10-line 20, p. 15-lines 15-35, p.21-22 and claims 16-36.

USPN 5,538,861 teaches anti-GAS6 antibodies that can be used to block GAS6 activation of Axl and cell growth. See col. 14-lines 25-60 and Fig. 10.

Jacob et al. teach that Axl is overexpressed in prostate carcinoma cell lines compared to normal prostate cells. See Abstract and Figure 2. Jacob et al. teach that the overexpression of Axl indicates a linkage between Axl expression and tumorigenesis and metastasis of the prostate. See p. 329-1st¶.

It would have been *prima facie* obvious at the time the invention was made to combine the teachings of USPN 5,538,861, WO 89/06692, and USPN 5,538,861 and use the antagonistic or cytotoxin labeled antibody to AXL of USPN 5,468,634 or the antagonistic GAS-6 antibody of USPN 5,538,861 to treat breast cancer with the methods WO 89/06692 because USPN 5,538,861 specifically points the methods WO 89/06692 for use of the therapeutic AXL antibodies and USPN 5,538,861 teaches that Axl is expressed in breast cancer. Additionally, given that WO 89/06692 teaches using antibodies to inhibit the growth factor receptor ligand for treatment of breast cancer and metastasis, it would have been obvious use the anti-GAS6 antibodies of USPN

5,538,861 for treatment. Furthermore, given that Jacob et al. teach the overexpression of AXL in prostate carcinoma cells and AXL's importance in tumorigenesis and metastasis of the prostate, it would have been obvious to perform the method on subjects with prostate cancer cells. Given the importance of developing new cancer therapeutics and given that the antagonistic AXL and Gas6 antibodies were taught in the art, one of skill in the art would have been motivated with a reasonable expectation of success of making and using the antibodies for treatment of cancer.

Although the references does not specifically state that the method is a method of reducing the invasivity of cancer cells, given that breast and prostate cancer patients are subjects in need of reduced invasivity of cancer cells and an inhibitor of the AXL protein/ligand is being administered to that population, the claimed method appears to be the same as the combined methods of the prior art, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claim Objections

12. Claim 10 is objected to because of the following informalities: The word "us" between the words "protein" and "selected" in the wherein clause should be "is". Appropriate correction is required.

13. All other objections and rejections recited in Office Action of November 3, 2009 are withdrawn.

14. No claims allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571)272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Helms Larry can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/
Primary Examiner, Art Unit 1642